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BULLETIN OF
MATHEMATICAL BIOPHYSICS
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THE HALF-LIFE OF A DRUG IN RELATION TO ITS THERAPEUTIC INDEX

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A procedure is given for the determination of the effective half-life of a drug *in vivo* with respect to an arbitrary response. If the half-life of the drug with respect to toxicity is different from that for therapy, the therapeutic index would be expected to depend on the temporal spacing of the dose. Equations are derived for this variation for a special case.

The stability of a drug in vivo cannot always be measured by direct biochemical analysis. It is possible to determine the half-life with respect to the production of a particular measureable response (mortality, respiratory stimulation, etc.). It is conceivable that the half-life with respect to a second response will be different if the second response occurs to some intermediate breakdown product chemically different from the one causing the first response. It is also conceivable that two or more breakdown products will exhibit varying potencies toward the first response. In such an instance the determination of true half-life is very complex. This latter possibility is omitted from the following considerations. What is always measured is the disappearance of potency with respect to a particular response.

Let $f(t)$ be defined as the ratio of potency after time t (in vivo) to the initial potency. If doses D_1 and D_2 are given t minutes apart (D_2 last) then the effective dose $E\bar{D}$ is $D_1 f(t) + D_2$, where E is measured in terms of a reference dose $\bar{D}$ (e.g., that giving 50% response in the population).

Suppose two identical, and instantaneous doses of magnitude $(2/3)\bar{D}$ are given at t minutes apart. Then $(2/3)\bar{D}f(t) + (2/3)\bar{D} = E(t)\bar{D}$. Since for $t = 0$, $E = 1.33$ and for $t = \infty$, $E = 0.67$ there must be some time interval $t = T$ for which $E = 1$ and hence $f(T) = 1/2$. Thus T is the effective half-life.

[1] This work was carried out under contract with the Medical Division of the Chemical Warfare Service.

The effective dose E produces the given response in a certain percentage of individuals P (or produces a certain percentage of standard response in all individuals). A direct plot between P and t can be made, and from this plot the half-life T is determined as the value for which $P = 50$ (e.g., 50% mortality) since then $E = 1\ \bar{D}$ (the LD–50) and $f = 1/2$. Percentages of response other than 50%, can of course be employed for determination of half-life.

It is very generally the case that a response to a drug is statistically distributed normally with respect to the logarithm of the dose. Let σ be the standard deviation (here the slope of the log concentration–mortality curve) and let $\bar{D}$ be the LD–50. Then if y is the deviate of the normal curve,

$$\sigma y = \log_{10} D/\bar{D}. \tag{1}$$

Taking the case in which $(2/3)\bar{D}$ is injected twice at t minutes apart, we have:

$$\sigma y = \log_{10} \frac{(2/3)\bar{D}f(t) + (2/3)\bar{D}}{\bar{D}} = \log_{10} [1 + f(t)] - 0.176. \tag{2}$$

If σ and $\bar{D}$ are known, then $f(t)$ can be determined from

$$f(t) = 10^{(\sigma y + 0.176)} - 1. \tag{3}$$

If the limiting factor is a monomolecular reaction, and if the doses can be considered instantaneous doses then

$$f(t) = 2^{-t/T}, \tag{4}$$

and

$$\sigma y = \log_{10}(1 + 2^{-t/T}) - 0.176. \tag{5}$$

From expression (5) we can determine for any σ the relation between y and t/T (the time measured in half-life units) and from this the percentage response P as a function of t/T. This transformation has been carried out for specific values of σ covering the values most commonly observed in toxicological work (Figure 1).

In this connection it may be pointed out that the slope on linear graph paper for the curve relating per cent response to dose in the neighborhood of $P = 50\%$ is approximately:

$$dP/d(\log_{10} D) = 40/\sigma, \tag{6}$$

while for $f(t) = 2^{-t/T}$

$$dP/d \log_{10} t = 9/\sigma. \tag{7}$$

Because of nonlinearity, the observed slopes are slightly less. Due to

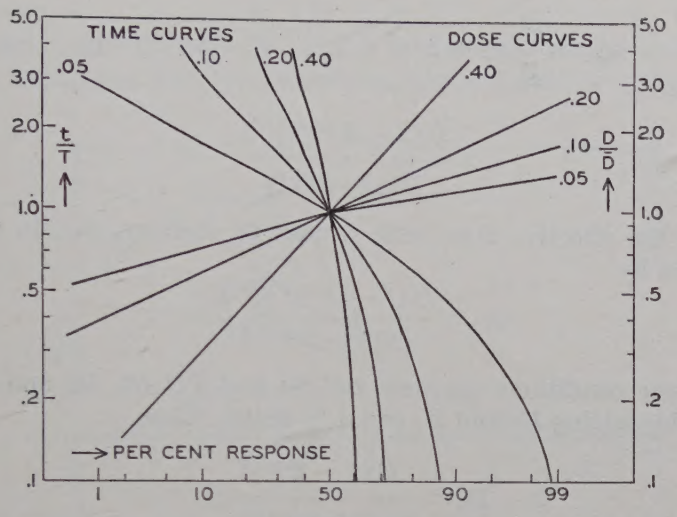

FIGURE 1

Theoretical curves for the per cent response as a function of dose for single doses, and as a function of time between application of two doses of magnitude 2/3 $\overline{D}$. The number for each is the value of the standard deviation, σ. The curves are on log–probability scale.

the great difference in the slopes, the standard error of the half-life will be much larger than that of the original *LD*–50.

In general it is possible to make the experimental determination of the half-life and check the *LD*–50 and σ simultaneously. This may reveal that the doses D_1 and D_2 used were not exactly 2/3 $\overline{D}$, in which case more general expressions than (2), (3), and (5) are required. These are respectively:

$$\sigma y = \log_{10}[rf(t) + B], \tag{8}$$

$$f(t) = r^{-1}\, 10^{\sigma y} - s/r, \tag{9}$$

$$\sigma y = \log_{10}(s + r\, 2^{-t/T}), \tag{10}$$

where r and s are the corrected fractions of the *LD*–50 applied, (r being the first). For substances stable in vitro $r = s$, unless different doses are used.

Consider only the case of a monomolecular breakdown so that $f(t) = 2^{-t/T}$. Let a drug have a *LD*–50 of $\overline{D}$ and *TD*–50 of D' so that its therapeutic index is $\overline{D}/D'$. Let the half-life with respect to mortality be T and that with respect to therapy be T'. Suppose that n doses are given Δ units of time apart. Then the effective dose with respect to mortality, E_L, in units of $\overline{D}$, is given by

$$E_L = \frac{D}{\bar{D}}\left(1 + 2^{-\Delta/T} + 2^{-2\Delta/T} + \cdots 2^{-(n-1)\Delta/T}\right)$$

$$= \frac{D\left(1 - 2^{-(n-1)\Delta/T}\right)}{\bar{D}\left(1 - 2^{-\Delta/T}\right)}. \tag{11}$$

Similarly the effective dose with respect to therapy, E_T, in units of D' is given by

$$E_T = \frac{D\left(1 - 2^{-(n-1)\Delta/T'}\right)}{D'\left(1 - 2^{-\Delta/T'}\right)}. \tag{12}$$

Under these conditions the new LD–50 and TD–50, D_n and D'_n are obtained by setting E_L and E_T equal to unity. Thus

$$\bar{D}_n = \frac{\bar{D}\left(1 - 2^{-\Delta/T}\right)}{\left(1 - 2^{-(n-1)\Delta/T}\right)}; \tag{13}$$

$$D'_n = \frac{D'\left(1 - 2^{-\Delta/T'}\right)}{\left(1 - 2^{-(n-1)\Delta/T'}\right)}. \tag{14}$$

Denoting by R_n the ratio of the therapeutic index for n doses given Δ units of time apart to the therapeutic index for single doses (or very widely spaced doses), we obtain:

$$R_n = \frac{\left(1 - 2^{-\Delta/T}\right)\left(1 - 2^{-(n-1)\Delta/T'}\right)}{\left(1 - 2^{-\Delta/T'}\right)\left(1 - 2^{-(n-1)\Delta/T}\right)}, \tag{15}$$

or for a very large number of repeated doses

$$R_\infty = \left(1 - 2^{-\Delta/T}\right) / \left(1 - 2^{-\Delta/T'}\right). \tag{16}$$

For continuous dosage $\Delta \to 0$, and R reaches a maximum or minimum value, given by R_m,

$$R_m = \frac{T'}{T}. \tag{17}$$

Equation (16) is illustrated in Figure 2.

If instead of equation (4) a more general expression $f(t)$ had been used, corresponding expressions could be derived instead of equations (11) – (17). The first of those would be of the forms $E_L\bar{D} = D[1 + f(\Delta) + f(2\Delta) + \cdots]$. The final result would be modified. If, for example, $f(t)$ can be approximated by a linear combination of two exponentials, then the maximum or minimum value of R_∞ does not

necessarily occur at $\Delta = 0$, but at some Δ depending on the values of the four time factors. The above results may be applicable to any case in which two different responses are initiated by a single agent.

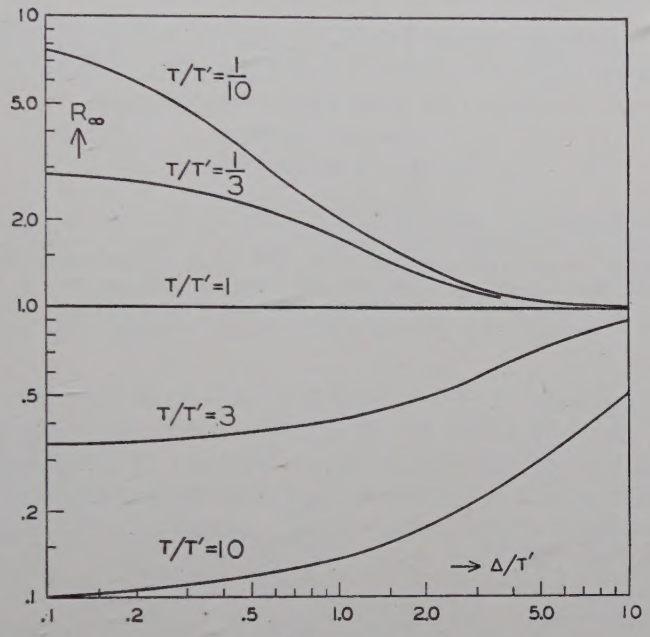

FIGURE 2

Theoretical curves for the relative therapeutic index (ratio of index for given spacing of doses to index for single dose) as a function of the temporal spacing of the doses. The time unit is the therapeutic half-life, T'. The curves are on log–log scale.

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CONTRIBUTIONS TO THE MATHEMATICAL THEORY OF THE STABILITY OF METABOLIZING SYSTEMS WITH VARIABLE SURFACE TENSION

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The paper investigates the stability of a metabolizing system subject to surface tension forces only. In line with some earlier work of N. Rashevsky, the surface tension is considered as a function of the concentration of the metabolite. Different theoretically interesting cases are discussed. The study indicates that surface tension forces alone are not likely to produce phenomena similar to those of cell division.

The work of H. D. Landahl (1942) and N. Rashevsky (1940) show the importance of the diffusion forces in cell division. In all the cases studied by H. D. Landahl and N. Rashevsky, the cell is assumed to have a constant surface tension, which always acts as a stabilizing factor, opposing cell division. In his earlier work, however, N. Rashevsky (1931) considered the possibility that the surface tension forces alone may produce a division of metabolizing systems, if the surface tension is assumed to be a function of the concentration of the metabolites. The lack of proper mathematical technique prevented a more detailed study of this mechanism at that time. Subsequent work on the role of diffusion forces in cell division threw the question into oblivion. However, since the approximation method, introduced later (Rashevsky, 1938) enables us now to treat the problem mathematically, Professor Rashevsky suggested the present study. While this study has now a purely theoretical interest, it contributes to the accepted view that surface phenomena alone are not adequate to account for cell division.

Experimental observations on the change of surface tension of a solution with changes in the concentration of the solution are well known (Bakker, 1928). For capillary active substances (those substances which tend to decrease the surface tension of the solution) the change of surface tension with concentration is much greater than for capillary inactive substances (those substances which tend to increase the surface tension). For this reason the former type of substance was chosen for this analysis. It is assumed that this substance exists in the environment of the metabolizing system at very small concentrations and that the relationship between the surface tension

of the system and the concentration of the substance can be approximated by the linear expression

$$\gamma = \gamma_o - Ac\,; \quad \text{for } \gamma > 0\,,$$

where $A > 0$.

With the same notations as those used by N. Rashevsky (1940), we have (Rashevsky, 1940, p. 42):

$$\frac{1}{r_1}\frac{dr_1}{dt} = \frac{1}{3\,\eta\,V}(I_1 + I_2)\,.$$

Since the I_1 represents the volume forces of the system due to the diffusion of the substance in question, and since it is assumed that this substance is found in the system only in very small concentrations, those volume forces due to its diffusion are negligibly small. This reduces the above equation to:

$$\frac{1}{r_1}\frac{dr_1}{dt} = \frac{1}{3\,\eta\,V} I_2.$$

The expression for the pressure due to surface tension forces (p_t) is given (Rashevsky, 1940) by $p_t = -\gamma(1/R_1 + 1/R_2)$ where R_1 and R_2 are the principle radii of curvature of the surface. Using N. Rashevsky's cell model and notation at the ends of the cell $R_1 = R_2 = r_2$ and at the sides of the cell $R_1 = r_1$ and $R_2 = r_2$. The pressure at the ends due to surface tension is given by $p_e = -2\gamma_1/r_2$ and at the sides, $p_s \doteq -\gamma_2(1/r_1 + 1/r_2)$, where γ_1 and γ_2 are the coefficients of the surface tension at the ends and sides of the cell, respectively.

With reference to the Betti equation, (Rashevsky, 1940, chapter iii), we have

$$xX_v + yY_v = \gamma_2 r_2\left(\frac{1}{r_1} + \frac{1}{r_2}\right) \qquad \text{(at sides)}$$

and

$$zZ_v = -\gamma_1 r_1 \frac{2}{r_2} \qquad \text{(at ends)}.$$

Therefore,

$$I_2 = -\gamma_1 r_1 \frac{2}{r_2} S_1 + \tfrac{1}{2}\gamma_2 r_2\left(\frac{1}{r_1} + \frac{1}{r_2}\right) S_2,$$

where S_1 and S_2 are the areas of the ends and sides of the cell, respectively, $S_1 = 2\,\pi\,r^2_2$ and $S_2 = 4\,\pi\,r_1\,r_2$. Substituting these values of S_1 and S_2 in the Betti equation gives

$$I_2 = -\gamma_1 r_1 \frac{2}{r_2} \times 2\,\pi\,r^2_2 + \tfrac{1}{2}\left[\,\gamma_2 r_2\left(\frac{1}{r_1} + \frac{1}{r_2}\right) 4\,\pi\,r_1\,r_2\,\right].$$

The volume of the cell, however, is given by ($V = 4/3\ \pi\ r_1\ r^2_2$). The above form of I_2 reduces to

$$I_2 = \frac{3}{2} V \left[\gamma_2 \left(\frac{1}{r_1} + \frac{1}{r_2} \right) - \gamma_1 \frac{2}{r_2} \right],$$

but $\frac{1}{r_1} \frac{dr_1}{dt} = \frac{1}{3\,\eta\,V} I_2$ for surface forces; hence,

$$\frac{1}{r_1} \frac{dr_1}{dt} = \frac{1}{2\,\eta} \left[\gamma_2 \left(\frac{1}{r_1} + \frac{1}{r_2} \right) - \gamma_1 \frac{2}{r_2} \right]. \tag{1}$$

It must be remembered, however, that γ_1 and γ_2 are given by the relations $\gamma_1 = \gamma_0 - Ac_1$ and $\gamma_2 = \gamma_0 - Ac_2$ where c_1 and c_2 are the concentrations of the substance at the ends and sides of the cell, respectively; hence equation (1) becomes

$$\frac{1}{r_1} \frac{dr_1}{dt} = \frac{1}{2\,\eta} \left[(\gamma_0 - Ac_2) \left(\frac{1}{r_1} + \frac{1}{r_2} \right) - (\gamma_0 - Ac_1) \frac{2}{r_2} \right]. \tag{2}$$

The next step in the analysis is to obtain c_1 and c_2 as functions of r_1, r_2, D_i, D_e, h, c_0, and q (using N. Rashevsky's notations), and to substitute these functions into equation (2). Using the approximation method, N. Rashevsky (1940, chap. i) obtains

$$c_1 = \frac{2(D_i D_e + \delta D_i h)\ \bar{c} + r_1 h D_e c_0}{2D_i D_e + 2\delta D_i h + r_1 h D_e},$$

and

$$c_2 = \frac{2(D_i D_e + \delta D_i h)\ \bar{c} + r_2 h D_e c_0}{2D_i D_e + 2\delta D_i h + r_2 h D_e},$$

where in the steady state, $\bar{c} = c_0 + \Lambda q$ and $\Lambda = f(r_1, r_2, h, \delta, D_i, D_e)$. For the sake of simplicity, let $h \to \infty$ and let

$$\Lambda' \equiv \lim_{h \to \infty} \Lambda, \quad \bar{c}' \equiv \lim_{h \to \infty} \bar{c}, \quad \delta \overset{\infty}{} r_2,$$

then $\bar{c}' = c_0 + \Lambda' q$. Also let $c'_1 \equiv \lim_{h \to \infty} c_1$ and $c'_2 \equiv \lim_{h \to \infty} c_2$.

Elementary methods yield

$$c'_1 = c_0 + \frac{2r_1 r^2_2}{3D_e} \times \frac{(2D_i + D_e) r_2}{2(2r_2 D_i + r_1 D_e) r_1 + (2D_i + D_e) r^2_2}\, q; \tag{3}$$

$$c'_2 = c_0 + \frac{2r_1 r^2_2}{3D_e} \times \frac{2r_2 D_i + r_1 D_e}{2(2r_2 D_i + r_1 D_e) r_1 + (2D_i + D_e) r^2_2}\, q. \tag{4}$$

Using equations (3) and (4), expression (2) becomes

$$\frac{1}{r_1}\frac{dr_1}{dt}=\frac{1}{2\eta}\left\{\left[\gamma_0-A\left(c_0+\frac{2r_1r^2_2}{3D_e}\times\right.\right.\right.$$
$$\left.\left.\left.\frac{2r_2D_i+r_1D_e}{2(2r_2D_i+r_1D_e)r_1+(2D_i+D_e)r^2_2}\,q\right)\right]\left(\frac{1}{r_1}+\frac{1}{r_2}\right)\right.$$
$$\left.-\left[\gamma_0-Ac_0+\left(\frac{2r_1r^2_2}{3D_e}\times\right.\right.\right.$$
$$\left.\left.\left.\frac{(2D_i+D_e)r_2}{2(2r_2D_i+r_1D_e)r_1+(2D_i+D_e)r^2_2}\,q\right)\right]\frac{2}{r_2}\right\}. \tag{5}$$

Equation (5) is a relation for the relative rate of elongation of the cell in the r_1 direction due to surface tension forces. When the right-hand side of this equation is positive, the cell is elongating. We shall now determine the conditions which must be imposed upon the parameters and variables of the equation, so that elongation will occur.

In order to greatly simplify the mathematical analysis, we assume that $D_e = D_i = D$. This assumption reduces equation (5) to:

$$\frac{1}{r_1}\frac{dr_1}{dt}=\frac{1}{2\eta}\left\{\left[\gamma_0-A\left(c_0+\frac{2r_1r^2_2}{3D}\times\frac{2r_2+r_1}{(4r_2+2r_1)r_1+3r^2_2}\,q\right)\right]\right.$$
$$\left(\frac{1}{r_1}+\frac{1}{r_2}\right) \tag{6}$$
$$\left.-\left[\gamma_0-A\left(c_0+\frac{2r_1r^2_2}{3D}\times\frac{3r_2}{(4r_2+2r_1)r_1+3r^2_2}\,q\right)\right]\frac{2}{r_2}\right\}.$$

At this point, note that when $r_1 = r_2$, $dr_1/dt = 0$, which is what we would expect from considerations of symmetry.

Let it be assumed that the substance is being consumed in the cell, i.e., $q < 0$.

To simplify the algebraic manipulation, consider the following notations:

$$\phi \equiv \gamma_0 - Ac_0$$

and

$$\omega \equiv \frac{2r_1r^2_2}{3D}\,\frac{|q|\,A}{(4r_2+2r_1)\,r_1+3r_2} > 0.$$

Substituting ω and ϕ into equation (6) gives:

$$\frac{1}{r_1}\frac{dr_1}{dt}=\frac{1}{2\eta}\left\{\left[\phi+(2r_2+r_1)\omega\right]\left(\frac{1}{r_1}+\frac{1}{r_2}\right)-[\phi+3r_2\omega]\frac{2}{r_2}\right\},$$

which can be simplified to:

$$\frac{1}{r_1}\frac{dr_1}{dt}=\frac{1}{2\eta}\left[\phi\left(\frac{1}{r_1}-\frac{1}{r_2}\right)+\omega\left(2\frac{r_2}{r_1}+\frac{r_1}{r_2}-3\right)\right] \tag{7}$$

Elongation implies $dr_1/dt > 0$. Therefore since $\eta > 0$, we have

$$\phi\left(\frac{1}{r_1}-\frac{1}{r_2}\right)+\omega\left(2\frac{r_2}{r_1}+\frac{r_1}{r_2}-3\right)>0.$$

Since $r_1 > r_2$, $1/r_1 - 1/r_2 < 0$, hence

$$\frac{2\frac{r_2}{r_1}+\frac{r_1}{r_2}-3}{\frac{1}{r_1}-\frac{1}{r_2}}\omega+\phi<0,$$

which can be simplified to

$$(2r_2-r_1)\,\omega+\phi<0. \tag{8}$$

CASE I, $\phi = 0$.

Relation (8) becomes

$$(2r_2-r_1)\,\omega<0,$$

or, $r_1 > 2r_2$ is a *necessary* and *sufficient* condition for elongation.

CASE II, $\phi > 0$.

Relation (8) becomes

$$(2r_2-r_1)\frac{\omega}{\phi}+1<0,$$

or, $r_1 > 2r_2$ is a *necessary* condition for elongation.

CASE III, $\phi < 0$.

Relation (8) becomes

$$(2r_2-r_1)\frac{\omega}{\phi}+1>0. \tag{9}$$

A *sufficient* condition for elongation is $r_1 \geqq 2r_2$. The necessary conditions are determined as follows: The volume V of the cell is given

by $V = 4/3\ \pi\ r_1\ r^2_2 = 4/3\ \pi\ r^3_0$ where $r_0 \equiv$ the radius which the cell would have if it were a sphere. Thus

$$r_1 = \frac{r^3_0}{r^2_2}.$$

Let $M \equiv \dfrac{q\ \ A}{3D(\gamma_0 - Ac_0)}$.

Substituting the functions of ω and ϕ into relation (9) and letting $r_1 = r^3_0/r^2_2$, we obtain

$$\frac{3}{2} r^{-3}_0\, r^6_2 - 2Mr^5_2 + 2r^3_2 + r^3_0\, Mr^2_2 + r^3_0 > 0\,. \tag{10}$$

Relation (10), defined only for $r_1 > r_0 > r_2$, is the necessary and sufficent condition for elongation. In order to investigate the stability of the cell when $r_2 \approx r_0$, let $r_2 = (r_0 - \Delta r_0)$ where $\Delta r_0 > 0$, then neglecting all infinitesimals beyond the first order, relation (10) becomes, after simplifying

$$-Mr^2_0\ (r_0 - 8\Delta r_0) + 4.5r_0 - 15\Delta r_0 > 0\ .$$

This implies that for $\Delta r_0 > 0$ and $\Delta r_0 \approx 0$

$$r_0 \approx \sqrt{\frac{4.5}{M}} \equiv L. \tag{11}$$

To summarize, if r_0 *is greater than* L, a slight elongation of the cell *will not* result in continued elongation. If, however, r_0 *is below the critical value* L, a slight elongation *will* result in continued elongation.

Related to the question of "deformation stability" in cells is the question of "configuration stability." That is to say, for what values of the parameters and variables would the surface energy (with respect to surface tension) of a cell of given volume be greater than the surface energy of the same volume in a two cell configuration?

This can be determined as follows:

From considerations of symmetry, when $r_1 = r_2$, equation (3) is equivalent to expression (4)

$$\lim_{\substack{r_1 \to r_2 \\ D_1 \to D_e}} c'_1 = \lim_{\substack{r_1 \to r_2 \\ D_1 \to D_e}} c'_2 \equiv c_s = c_0 - \frac{2|q|}{9D} r^2_0.$$

Also for a sphere, $\gamma_1 = \gamma_2 = \gamma_0 - Ac_s$; therefore,

$$\gamma = \gamma_0 - A\left(c_0 - \frac{2}{9}\frac{|q|}{D} r^2_0\right). \tag{12}$$

$E_1 \equiv$ Surface energy for a one cell configuration.

$E_2 \equiv$ Surface energy for a two cell configuration.

We require that the two cell configuration be more stable than the one cell state. Thus,

$$E_1 > E_2, \tag{13}$$

but

$$E_1 = 4\pi r^2_0 \gamma = 4\pi r^2_0 \left[\gamma_0 - A\left(c_0 - \frac{2}{9}\frac{|q|}{D} r^2_0\right)\right],$$

and since r for the two cell state is given by $r \cong .8 r_0$,

$$E_2 = 2\left\{4\pi \times .8^2 r^2_0 \left[\gamma_0 - A\left(c_0 - \frac{2}{9}\frac{|q|}{D} .8^2 r^2_0\right)\right]\right\}.$$

Substituting the values of E_1 and E_2 into relation (13) and simplifying, we obtain

$$\phi - \frac{2}{9} A \frac{|q|}{D} .64 r^2_0 < 0;$$

$$r^2_0 > -\frac{2.34}{|M|} \text{ for } \phi < 0;$$

$$r^2_0 > \frac{2.34}{|M|} \text{ for } \phi > 0.$$

In summary, when $\phi < 0$, the two cell configuration is always more stable than the one cell state. When $\phi > 0$, however, the two cell state is more stable only when r_0 is smaller than a certain maximal value. By identical methods the case $q > 0$, i.e., production of a surface active substance has also been studied.

The following table is a brief summary of all conclusions which can be drawn from the analysis:

	Value of ϕ	Will cell start to elongate?	Is two cell configuration more stable?
Substance Consumed ($q < 0$)	$\phi = 0$	Not unless $r_1 > 2r_2$	Yes
	$\phi > 0$	Not unless $r_1 > 2r_2$	Not unless $r_0 > \sqrt{-\frac{2.34}{M}}$
	$\phi < 0$	Yes, unless $r_0 < \sqrt{\frac{4.5}{M}}$	Yes
Substance Produced ($q > 0$)	$\phi = 0$	Yes, unless $r_1 > 2r_2$	No
	$\phi > 0$	Yes, unless $r_1 > 2r_2$	Yes
	$\phi < 0$	Physically unattainable	

Of the several combinations tabulated above, two are of especial interest: choices of q and ϕ which will allow both shape and configurational stability and choices of q and ϕ which will allow neither. The biological significance of these alternatives is as follows: If we imagine that surface forces have *nothing* to do with cell division, then, for the best arrangement, the cell division mechanism, whatever it may be, should transform the system from one doubly* stable state to another doubly stable state. It therefore becomes interesting to know if such states are indeed attainable. On the other hand, if we imagine that surface forces have *everything* to do with division we must inquire first if doubly unstable cases are at all attainable, it being supposed that lengthening is indispensable for cleavage (Gray, 1922). However, the possibility of double instability is not the only attribute of a satisfactory cell division hypothesis. The additional requirement is that the double instability be attained only after the cell has exceeded a critical size. Our second problem therefore is to investigate the existence of double instability above certain cell sizes.

What we have called configurational stability is a special case of thermodynamic stability wherein the free energy consists only of

* i.e., with respect to shape and configuration stability.

one term, i.e., that for the free energy of the surface. It can be seen from Table 1 that for $q < 0$, the system is thermodynamically stable only when $\phi > 0$ and $0 < r_0 \leqq \sqrt{-2.34/M}$. It may be asked whether there are various shapes (i.e. various equilibrium points with respect to changing shape) consistent with this restriction. Equilibrium with respect to changing shape requires that relation (10) be an equation. Putting $\beta = r_2/r_0$ into relation (10) as an equation, we find

$$r_0 = \left(\frac{3\beta^6 + 4\beta^3 + 2}{2M\beta^2(1-2\beta^3)}\right)^{1/2}, \quad \sqrt[3]{\tfrac{1}{2}} < \beta < 1. \tag{14}$$

The general shape of this curve can be deduced from the fact that, r_0 becomes infinitely great at the left end of the curve ($\beta \to \sqrt[3]{\frac{1}{2}}$ and $r_0 = \kappa > 0$ when $\beta \to 1$. At these points, the derivative

$$\frac{dr_0}{d\beta} = \frac{1}{2r_0\beta(1-2\beta^3)}\left\{3\beta(3\beta^3+2) - 2r^2{}_0 M(1-5\beta^3)\right\} \tag{15}$$

is respectively large and negative ($\beta \to \sqrt[3]{\frac{1}{2}}$) and negative when $\beta \to 1$.

By setting expression (15) equal to zero, we obtain

$$f(\beta) = 3\beta^3 - 14\beta^6 - 12\beta^3 + 2 = 0. \tag{16}$$

The quantity $f(\beta)$ is an odd function and has two changes in sign, hence it can have but one zero in the range of β. This means that r_0 plotted against β is roughly of the shape of a half U having an asymptote at $\beta = \sqrt[3]{\frac{1}{2}}$ and a positive value κ at $\beta = 1$.

The coexistence of shape and thermodynamic stabilities may now be ascertained by finding if it is possible for the curve (14) to intersect the straight line parallel to the β–axis,

$$r_0 = \left(-\frac{2.34}{M}\right)^{1/2}. \tag{17}$$

By equating expressions (14) and (17) we obtain

$$3\beta^6 - 9.36\beta^5 + 4\beta^3 + 4.68\beta^2 + 2 = 0 \tag{18}$$

as the condition for the intersection of expressions (14) and (17). It can readily be seen that equation (18) has no positive roots for $\sqrt[3]{\frac{1}{2}} < \beta < 1$, hence the shape, and the thermodynamic stability can never coexist for this case. This result need not preclude the occurrence of thermodynamically unstable shapes (non-spherical) if the process of division, whatever be its nature, has a high energy of activation.

For the case when $q > 0$ and $\phi = 0$, the cell is in equilibrium with respect to shape change when relation (8) becomes an equation with $\phi = 0$, i.e.,

$$\beta = (\tfrac{1}{2})^{1/3}. \tag{19}$$

Since for this case, the system is always thermodynamically stable, all cells satisfying equation (19) will be stable with respect to both shape and configuration.

The first question posed above can therefore be answered in the affirmative. Double stability throughout a range of shapes is unequivocally attainable for $q > 0$ and $\phi = 0$. There is a slight chance that it would be attainable for $q < 0$; $0 < r_0 < \sqrt{-2.34/M}$.

The answer to the second question is obvious from inspection of Table 1. The only possible combination for double instability ($q > 0$; $\phi > 0$) operates *below* a critical state, rather than above, as would be required of a satisfactory division mechanism.

Conclusions. It is generally agreed upon that any analysis of the mechanism of division must take into account several contributing factors, whose resultant effect is the phenomenon of cell division. Observation on the structure and division of different "kinds" of cells leave no doubt that those various contributing factors are rarely if ever present in the same "proportions" in any two kinds of dividing cells.

A question early raised in connection with this work is: which of these factors, if any, is the dominant one in cell division? One approach to the answer of this question is the analysis of each of the apparently important factors separately with the assumption that it alone could at least qualitatively account for the phenomenon. In the present paper, using the above approach, we start out with the assumption that surface tension is this dominant force. It has been required simply that surface tension effects would account for the elongation and thermodynamic instability of cells above certain critical sizes. Any additional mechanisms which would be required to explain the transition from the thermodynamically unstable elongated cell to the two cell state have been tacitly assumed to operate. The analysis leads to the conclusion that surface tension forces, in spite of these additional sympathetic assumptions, do not account for the process of cell division. This conclusion is in complete agreement with other theoretical and experimental evidence, chief of which is the extremely low tension at cell surfaces measured by recent workers (Bourne, 1942).

It should be noted, in closing, that the conclusions to which we have been led are necessarily dependent upon the nature of the ideal

system we have assumed. A subsequent analysis should certainly proceed without the following of the assumptions made here: infinite permeability to the surface active solute, zero adsorption of the solute at the cell boundary, and constant rate of metabolism. Ultimately, of course, the theoretical scheme must be patterned after what is known regarding the metabolism of surface active agents within cells.

The many valuable suggestions offered by Dr. M. Morales and Professor N. Rashevsky greatly facilitated the writing of this paper.

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ASYNCHRONY OF LABYRINTHINE RECEPTORS AS A PHYSICAL FACTOR IN MOTION SICKNESS

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Evidence is presented to show that despite their effectiveness in producing motion sickness the actual frequencies and accelerations involved in ship motion are rather low. It is suggested that the disparity is due to the fact that ship motion is such as to cause an asynchrony between signals from the labyrinth and those from other motion receptors.

Introduction. In order to obtain an incidence of motion sickness among the test population comparable to that aboard ships, experimental devices operate at peak accelerations of 1g (980 cms sec^{-2}) or more, and at frequencies in considerable excess of ship oscillations. A comparison of these values with real ship motions can be made assuming that the latter are simple harmonic in both roll and pitch (Fig. 1). Such computations have been made for certain positions

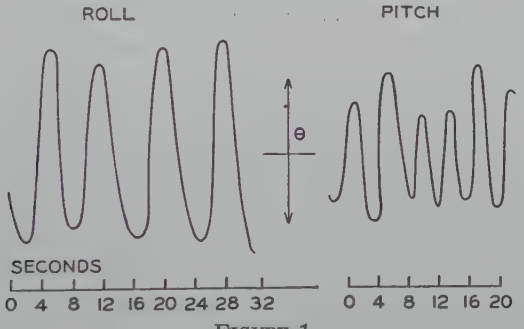

FIGURE 1

Simultaneous records of roll and pitch taken from unpublished observations aboard the U.S.S. *Washington* (BB 56).

aboard several classes of naval vessels (Table 1). The amplitudes used are from sallying data, and can be considered as absolute upper limits; nevertheless it will be observed that the average peak accelerations developed are well below 1g.[1] This disparity in the effective-

[1] It is not intended to give the impression that the peak value of the acceleration is not an etiological factor; only that it is not the sole factor. The order of vessels in Table 1 (descending order of accelerations) is almost precisely the order of decreasing effectiveness in producing seasickness among the crews.

TABLE 1

Vessel Type	Period of Roll (Seconds)	Amplitude of Roll (Degrees)	Period of Pitch (Seconds)	Amplitude of Pitch (Degrees)	Average Acceleration
Destroyer	9.5	25	5	5	.26 g
LCI	4.5	25	3	5	.21 g
LST	5.0	15	4	3	.19 g
Destroyer Escort	8.0	25	5	5	.14 g
Heavy Cruiser	12.0	20	7	4	.14 g
Carrier	16.0	15	7	4	.13 g
Light Cruiser	12.0	20	7	4	.13 g
Escort Carrier	13.0	20	7	4	.12 g
Battleship	14.0	12	6	3	.12 g
Transport	14.0	25	7	4	.08 g

This table is constructed entirely from unrestricted information. The periods and amplitudes are average values kindly furnished the author by the Bureau of Ships, Navy Department. The "average acceleration" is the arithmetic mean of the roll and pitch contributions at three points aboard the vessel: at the bow on the water line, abeam of midships on the water line, and high on the foremast.

ness of experimental devices and real ships naturally suggests that the shipboard motion has certain additional features not yet incorporated into the devices, or, at least not in the proper quantitative manner. Ultimately such features must be related to the characteristics of the peripheral and central mechanisms by which the organism perceives the motion. This paper is concerned with features which appear to be directly related to the mechanics of the labyrinthine receptors. It must of course be recognized that in addition to the question of effective stimulation, motion sickness poses the problem of how the stimulation operates to fire off the visceral responses. This second question undoubtedly involves central phenomena (E. A. Spiegel, 1944), and no attempt is made here to establish a liaison between the two questions.

There can be little doubt, especially since the study of A. Sjöberg, (1931), that labyrinthine, visual, and proprioceptive stimulation each play partial roles in the etiology of seasickness. A. Sjöberg demonstrated this by excluding these sources of information, one at a time, but it is reasonable to suppose that *asynchrony* of one receptor with respect to another would likewise affect adversely the ability to resist the sickness. The asynchrony might be described as a situation in which "coordination is difficult" and although this description is vague with respect to the central *mechanism* of "coordination," it expresses

incontestable experimental facts. The asynchrony proposed here as an etiological factor is chiefly that which can arise between labyrinthine mechanisms and those of other receptors. More specifically, there is comparatively little time lag between the application of a variable external stimulus and the variable physiological response in the sensory fibers from the eye or from proprioceptors. If θ is the instantaneous angle of a periodic roll or pitch, it may be assumed that the frequencies in such fibers are in phase with θ. This may or may not be the case for the labyrinth, as will be discussed below.

Mechanical Considerations Regarding the Canals. The discussion of this section for the most part derives its factual information from the beautiful experiments of G. Schmaltz (1931) on man, W. Steinhausen (1933) on the pike, and O. Löwenstein and A. Sand (1940) on the ray; therefore at the outset the dangers attending transspecific analogy must be acknowledged.

G. Schmaltz and W. Steinhausen have established that for mechanical purposes a semicircular canal—in particular, the horizontal—can be treated as a rigid toroidal container filled with a fluid of definite viscosity. It is here assumed that the remaining canals can likewise be schematized.[2] Into the lumen of the canal, at the ampulla, extends the cupula, much as a gate hinged at the crista, containing the nerve endings and with them constituting the end organ.

Consider now the rotation of the canal about an arbitrary axis normal to its plane. Two simple but important facts can be readily shown: (a) The forces acting to rotate the fluid within the canal are determined exclusively by the components of the acceleration normal to the radius of gyration, and (b) The effect of these forces on the fluid will be the same as though the canal were being rotated with a similar motion about its own axis of symmetry. These circumstances make it easy to describe the motion of the endolymph as the whole organism is being rotated about a distant axis (the usual experimental situation).

If ω and ω_E are respectively the angular velocities of the canal and of the contained endolymph, and μ is the coefficient of friction calculated from Poiseuille's Law, then it can be shown that,

$$\frac{d\omega_E}{dt} = \mu(\omega - \omega_E). \qquad (1)$$

If the viscosity coefficient and density of endolymph are taken as equal

[2] For the thesis developed in this paper it is only necessary that the pattern of discharge in all three canals be affected in the same way by the physical stimulus. However, it should be emphasized that corresponding central effects may be (and, on physiological evidence, likely are) different for the three canals.

to those of water, and the radius of the canal is taken as 2×10^{-2} cms, then μ is 200 sec^{-1}.

Equation (1) can be integrated for various motions imposed on the canal to discover the corresponding motion of the endolymph. Three of these are of experimental interest: I. The canal is rotated at a constant angular velocity, starting from rest. II. The canal is accelerated angularly at a constant rate, starting from rest, and III. The canal is oscillated in angular simple harmonic motion ($\theta = \theta_0 \sin \omega t$). In each of these cases there will be a certain pressure over any cross section of the endolymph, i.e., the pressure which would act on any structure fixed rigidly to the canal and extending into the endolymph. These pressures, P_{I}, P_{II}, and P_{III}, are given by the product of P_0, a constant common to all cases, a constant determined by the particular experimental conditions, and a time dependent factor, thus,

$$P_{\text{I}} = P_0 P_1 e^{-\mu t}, \tag{2}$$

$$P_{\text{II}} = P_0 P_2 (1 - e^{-\mu t}), \tag{3}$$

$$P_{\text{III}} = -P_0 P_3 \cos(\omega t + \phi), \quad (\phi = \tan^{-1} \frac{\mu}{\omega}). \tag{4}$$

Recalling that μ is 200, it is evident that in case I, the pressure on any structure will vanish very fast. In case II it will attain a constant value very fast. The angular velocity, ω, imposed by ship motion is of the order of 1 sec^{-1} so that in case III ϕ is an angle very near 90°, or $P_{\text{III}} \cong P_0 P_3 \sin \omega t$, i.e., the pressure is almost exactly in phase with the imposed motion. The third case has never been tested experimentally, but the conclusions regarding the first two have been verified by G. Schmaltz. W. Steinhausen recognized that this general synchrony between the imposed motion and the endolymphatic motion precluded the explanation of persistence phenomena, such as a 20 second nystagmus, in terms of fluid movement. In resolving the difficulty he suggested that the site of persistence phenomena might be the cupula itself, in the sense that it deflected as a damped vibrator. W. Steinhausen convincingly proved this hypothesis by direct observation on the pike, showing that under experimental condition I the cupula is rapidly deflected from rest and returns slowly to the original position some 20 seconds later. Unfortunately Steinhausen's analysis appears to assume a "rigid linkage" between endolymph and cupula, and thus to contradict his experiments. Rectification is easy, however. We need only consider the deflection of a damped vibrator under the influence of the imposed force functions given by equations (2) – (4). Strictly speaking, the force on the cupula is proportional to these expressions and to the cosine of the angle through which the

structure is deflected, but if we limit ourselves to deflections of less than 25°, the cosine can be taken as unity. Integration of the equation of motion then leads to expressions for cupular angle of deflection $\psi(t)$ for each of the three experimental situations. Since there is no available data on $\psi(t)$ itself, but only O. Löwenstein and A. Sand's measurements on the change in resting frequency of discharge in the ampullar nerve, $\nu(t) - \nu_0$, the theoretical predictions cannot be tested without an additional hypothesis regarding the relationship between cupular deflection and nerve response. The assumption made here and justified *a posteriori* is that the per cent change in frequency of nerve discharge is proportional to the angle of deflection from rest. If this is the case, then $\nu(t)$ and $\psi(t)$ should be curves of the same general form and they appear to be so (see Löwenstein and Sand's discussion). The analytic relationship would be $\nu(t) - \nu_0 = h\nu_0\,\psi(t)$, where h is a proportionality constant.

Taking 2λ and κ^2 as gross coefficients of friction and elasticity respectively, it can be shown by straightforward methods that,

$$\psi_{\mathrm{I}} = \frac{P_0 P_I}{\kappa^2 - 2\lambda\mu + \mu^2} \frac{\mu}{r_1 - r_2} (e^{r_1 t} - e^{r_2 t}), \tag{5}$$

where $r_1 = -\lambda + \sqrt{\lambda^2 - \kappa^2}$ and $r_2 = -\lambda - \sqrt{\lambda^2 - \kappa^2}$. This function has the well known properties of a rapid ascent, passage through a maximum, and an elongated return to zero, as demanded by the experimental data for the case. When fitted in the usual way to O. Löwenstein and A. Sand's data (p. 270, Fig. 9), it is found that $r_1 = -.053$, and $r_2 = -10.6$, and these values are independent of the maximum ψ attained. Using this r_1 and r_2 it is found next that,

$$\psi_{\mathrm{II}} = 1.78\, P_0 P_2 (1 - e^{-.053t}) \cong .0944\, P_0 P_2\, t, \tag{6}$$

the linearity holding very accurately for the first five seconds. Since $P_2 = \alpha/\mu$, equation (4) states that within the first five seconds ψ is proportional to the angular acceleration and to the time. Again this is in good agreement (*ibid* p. 269, Fig. 8). However, curve fitting is not weighty evidence *per se*. A good cross check can be obtained by taking P_0 from the data of case II and using it to calculate the maximum ψ in case I. This calculated maximum (28.4 sec^{-1}) is in good agreement with that given by the experimental data of case I (26.0 sec^{-1}).

With these damping characteristics of the cupula extracted from the data for cases I and II, we can now predict the pattern of the discharge in the ampullar nerve when the canal is subjected to the

sinusoidal motion, $\theta = \theta_0 \sin \omega t$. For case III the equation of motion gives,

$$(\nu - \nu_0) = \text{Constant} \times \cos(\omega t + \phi + \xi), \tag{7}$$

where

$$\xi = \tan^{-1} \frac{2\lambda\omega}{\omega^2 - \kappa^2}. \tag{8}$$

It has already been stated that $\phi \cong 90°$, consequently if ξ were zero, equation (7) would predict that the ampullar discharge would be in phase with the angular displacement, θ. On the other hand, the discharge would be maximally out of phase for $\xi \cong 90°$. Thus ξ measures the asynchrony. Equation (8) shows how ξ depends on the elasticity and friction of the cupula and (noting that the period of the imposed vibration, $T = 2\pi/\omega$) on the period of the imposed vibration. Figure 2, which is a plot of ξ vs. T using the experimental values of r_1 and

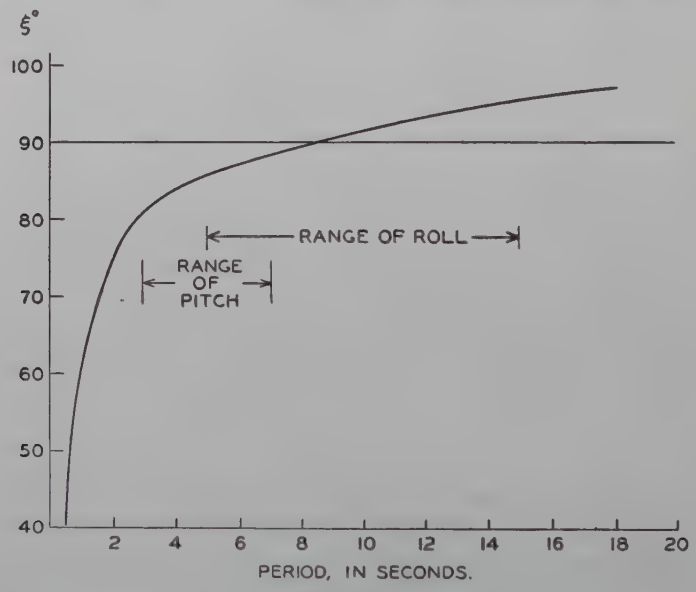

FIGURE 2

Plot of the period of the imposed motion vs. the phase angle, ξ of the cupula $\xi = 90°$ indicates maximum asynchrony. The ranges of roll and pitch for major naval vessels are indicated by arrows.

r_2 and the relations $r_1 + r_2 = -2\lambda$; $r_1 r_2 = \kappa^2$, shows that *asynchrony is maximal for a range of periods precisely equal to the periods of roll and pitch of large vessels.* When T is increased the asynchrony drops too, although slowly. (However when T is increased the amplitude is decreasing so that very likely there is no problem anyway.) Thus it

appears, if the present suggestion is correct, that so far as the canals are concerned, vessels are constructed so as to maximize the confusion of their passengers.

Mechanical Considerations Regarding Component Receptors. The discussion of the first section has been concerned exclusively with the mechanics of semicircular canals. The remaining labyrinthine receptors are presumably the utricles. Their precise mechanism appears to be unknown, but their anatomy suggests that, unlike the canals, they are stimulated by one of the principal components (horizontal and vertical) of the imposed motion. It will be shown in this section that these components are in phase with θ for certain amplitudes and positions aboard the vessel and are out of phase for others.

Consider the roll of the vessel schematized in Figure 3, where P

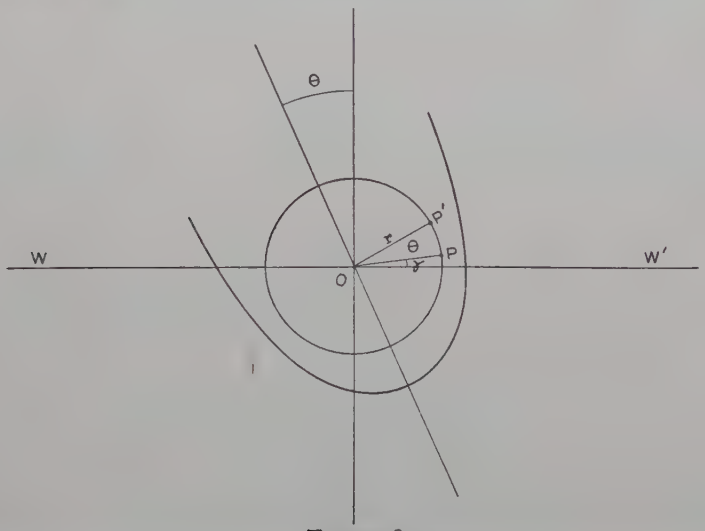

FIGURE 3
Motion of a Point, P, which is at position angle, γ, when the hull is level.

is some point fixed on a cross section through the hull. R is the distance from P to the axis of rotation, O. When the vessel is at the equilibrium position, the position angle of P is γ. As the vessel rolls, therefore, the coordinates of P are given by:

$$x = R\cos(\theta + \gamma), \tag{9}$$

$$y = R\sin(\theta + \gamma). \tag{10}$$

The horizontal and vertical components of the force are of course proportional to d^2x/dt^2 and d^2y/dt^2, and these can be found from equations (9) and (10) under the assumption that the ship rolls in angu-

lar simple harmonic motion, $\theta = \theta_0 \sin \omega t$. The times at which these force components reach a maximum or minimum can be found by setting equal to zero the third derivatives of x and y, and solving for the corresponding t. When this is done, it is found that for any one position angle, the horizontal force stays in phase with θ unless the amplitude, θ_0, exceeds a certain critical value θ^*. The critical amplitude varies with γ, i.e., with position aboard the vessel. Likewise, the vertical force stays in phase with θ unless θ_0 exceeds θ^{**}, in which case it falls out of phase during the first half of the cycle. If θ_0 is increased still more, to the point where it exceeds a second critical value θ^{***}, then an asynchrony develops during the second half of the cycle as well. Again, θ^{**} and θ^{***} vary with position aboard the vessel, i.e., with γ. These relationships are best understood from Figures 4 and 5. Illustrative wave forms are shown in Figure 6.

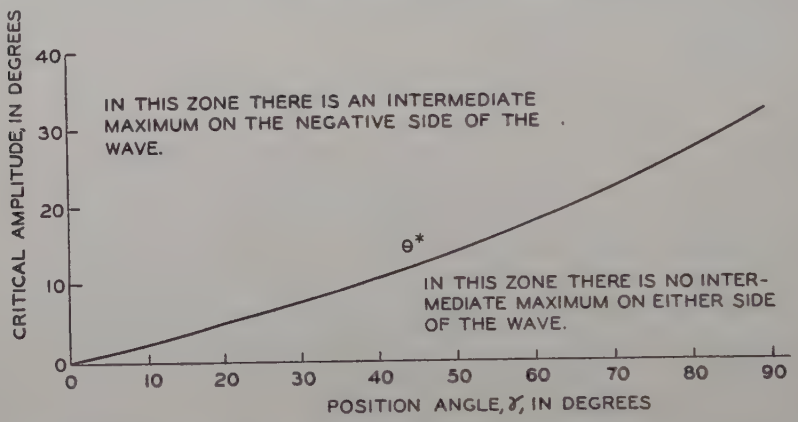

FIGURE 4

Critical angle (θ^*) for fundamental changes in the horizontal acceleration wave form, as a function of position angle, (γ).

It appears from the foregoing considerations that a receptor sensitive to horizontal or vertical components of the force developed in a roll may or may not be synchronous with receptors such as the eye or the proprioceptors, which are almost exactly in phase with θ. In this respect such receptors resemble the semicircular canals. An additional complication arises, however, in that the asynchrony for component receptors varies with position aboard the ship.

Discussion. If the hypothesis made in this paper to the effect that asynchrony between various receptors is one of the major factors which induce seasickness, then it appears that shipboard motion may owe some of its effectiveness to the fact that it imposes an asynchrony both on receptors which respond to circular flow of fluid and to those

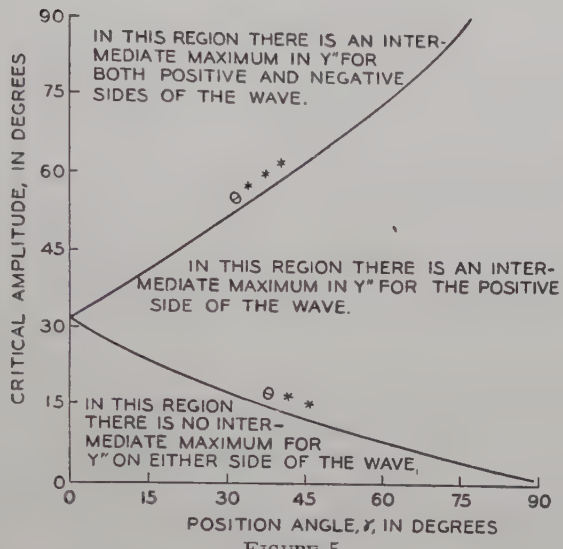

FIGURE 5

Critical angles for fundamental changes in the vertical acceleration wave forms, as a function of position angle, γ.

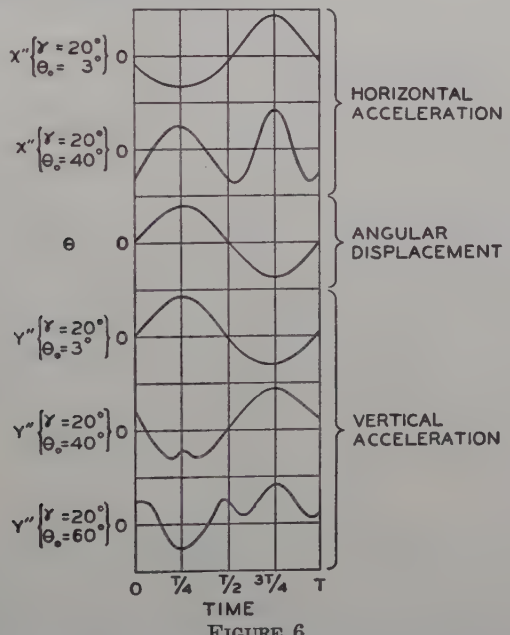

FIGURE 6

Schematic theoretical time variations of linear acceleration to illustrate wave forms for different combinations of amplitude and position angle. Upper curves are for horizontal components; lower curves for vertical components. The vertical dimensions have all been set so as to keep maximal heights the same regardless of actual magnitude.

which respond just to particular components of the imposed motion. In the former case it appears further that, with pitch–roll periods as they are and mechanical constants of the cupula as they are, shipboard motion actually maximizes the asynchrony.

In the past, rocking devices, swings, and elevators designed to study seasickness experimentally have seldom been constructed so as to reproduce accurately real shipboard motion. Accurate reproduction may be rather essential in view of the foregoing results. Records of ship motion (e.g., Fig. 1) can be made routinely aboard naval vessels, using fire–control equipment[3] and these wave forms may then be reproduced by the device. Aside from obtaining wave forms which cause asynchrony, there are preserved other features which may be of etiological importance. Among these is the fact noted in unpublished measurements of the author that a stormy sea as contrasted with a calm sea can be characterized just as well by a greater *spread* in amplitudes as by a greater average amplitude. This erraticity would seem to hinder any progressive adaptation.

In closing may be mentioned a problem suggested by cupular mechanics but one which may have some importance in general sensory physiology. The integral, $\int |\psi| dt$, measures in a sense the total stimulation which the canal receives, and it may be asked, what *wave form of the imposed force* will maximize this integral? This is clearly a problem in the calculus of variations, but it is one of whose solution the writer is not aware (and one which the writer has not solved). The solution must be something akin to sinusoidal motion for the reasons which O. Löwenstein and A. Sand discuss. A related problem is to find the wave form of the imposed forces such that ψ will have a given form. This can in many cases be done, and the results may be of some use in further experimental studies.

In the preparation of this manuscript the writer has had the helpful counsel of Professor Spiegel of Temple University and Professors Andrews and Kleitman of the University of Chicago. Certain of the work in the second section appeared in a Navy report with Mr. James Birren (1945).

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[3] This suggestion was made to the author by Captain J. Ormondroyd, and tried successfully during a cruise of the U.S.S. *Washington*.

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A MATHEMATICAL DESCRIPTION OF METABOLIZING SYSTEMS I

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An integral equation is established applicable to many types of metabolizing systems. The equation is applied to first order chemical reactions and to some biological systems.

A metabolizing system usually presents so many variables that a mathematical description is either impossible or crudely approximate. By neglecting some of the details of such systems, a satisfactory description, preserving important features, is possible through integral equations. The types of equations encountered are fortunately well known in mathematics. Thus if the description is adequate for the biological problem, the treatment will open a broad range of mathematics to the biophysicist for treating metabolizing systems.

The Integral Equation: For our purposes, a metabolizing system is any localized region where a substance or material is being consumed, produced, transported, modified, or stored. The system may be performing all or several of these functions simultaneously. In general, the system must have some defined boundary in order that experimental results may be obtained. In theory, however, a physical boundary need not exist.

A general metabolizing system may be pictured as an irregularly shaped region of complex structure into which material is entering, in which some material is being produced or consumed or stored, and some may be leaving by diffusion through the walls or by flow through openings. We introduce the following symbols:

$M(0)$ = amount of the metabolite present initially, $t = 0$.
$M(t)$ = amount of the metabolite present at time, t.
$R(\theta)$ = rate at which the metabolite is accumulating in the system.
$F(t)$ = the "metabolizing" function, to be defined presently.

In this region of irregular geometric shape, we are interested in some metabolite originally present in amount, $M(0)$. This metabolite

is accumulating at a rate $R(\theta)$ so that the amount accumulated in time interval $d\theta$ is $R(\theta)d\theta$. This additional amount suffers the fate of the original; it is metabolized. We introduce a "metabolizing" function defined as that function which will multiply the original amount, $M(0)$, to yield what remains of it at time, t. That is, the amount remaining from the original amount at time, t, is $M(0)\ F(t)$; the amount entering in the interval, θ to $\theta + d\theta$, which remains at time, t, is $F(t-\theta)\ R(\theta)\ d\theta$. The total amount present at time, t, from both these contributions is $M(t)$ which is seen to equal

$$M(t) = M(0)\ F(t) + \int_0^t R(\theta)\ F(t-\theta)\ d\theta. \qquad (1)$$

This equation is similar to some treated in population studies (V. Volterra and U. D'Ancona, 1935; A. J. Lotka, 1939) and is almost identical with one used by R. V. Churchill (1944) in another problem.

Whether equation (1) is an integral equation of the first or second kind depends upon the information we have of the system. The most likely situation experimentally is that we know $M(0)$ and can determine $M(t)$, then if we can control or determine R, the equation is a Volterra integral equation of the second kind in $F(t)$. Occasionally the information will be such that R is the unknown, then equation (1) is a Volterra integral equation of the first kind in R (H. Margenau and G. M. Murphy, 1943). Finally if $M(0)$, R, and F are known, the equation can be integrated either directly or numerically to find $M(t)$.

Applications to some chemical and biological systems: A large number of biological and chemical systems are characterized by the fact that the rate of reaction of the substance of interest is directly proportional to the quantity of the reacting substance present. This type of reaction is designated in chemical kinetics as a first order reaction. As a numerical example, we can consider the decomposition of dibromosuccinic acid in hot water investigated by Van't Hoff and treated by F. L. Hitchcock and C. S. Robinson (1936).

All first order reactions are very easily treated by equation (1) with the following designations:

$M(0) =$ a known constant.
$F(t) = F(0) = 1$.
$R(\theta) = -k\,M(\theta)$.

Equation (1) becomes

$$M(t) = M(0) - k \int_0^t M(\theta)\ d\theta. \qquad (2)$$

Equation (2) is of the type

$$\phi(x) = f(x) + \lambda \int_0^t K(x, z)\, \phi(z)\, dz.$$

This Volterra equation of the second kind is solved by the Liouville–Neumann series (Margenau and Murphy, 1943),

$$\phi(x) = \sum_{n=0}^{\infty} \lambda^n \phi_n(x)$$

provided

$$\phi_0(x) = f(x)\,; \phi_1(x) = \int K(x, z)\, \phi_0(z)\, dz; \cdots \phi_n(x) = \int K(x, z)\, \phi_{n-1}(z)\, dz.$$

In our example, $K(x, z) = 1$, $\lambda = -k$, and $\phi_0(x) = M(0)$. Introducing these expressions and integrating, we have

$$M(t) = M(0) \sum_{n=0}^{\infty} \frac{(-kt)^n}{n!} = M(0)\, e^{-kt}. \qquad (3)$$

Equation (3) is the usual exponential expression which is more easily obtained in this instance by stating the relation in differential equation form and integrating. With $k = 0.030$, the equation is an adequate description of the decomposition of dibromosuccinic acid in the Van't Hoff experiment.

First order reactions in certain systems, however, seem possible of treatment in much more elegant manner through equation (1) than through differential equations. As an example, let us consider a system in which the reaction is of the first order and at the same time the material is flowing out constantly such that the "metabolizing" function is of the form $F(t) = (1 - ct)$. Using the designations as in equation (2) we have

$$M(t) = M(0)\, (1 - ct) - k \int_0^t M(\theta)\, [1 - c(t - \theta)]\, d\theta. \qquad (4)$$

This integral equation may be solved by the Liouville–Neumann series as used in equation (2), however, it is desirable to introduce the powerful mathematical technique of the Laplace transform which is eminently suited for treating many of the problems described through equation (1).

The integral on the right of equation (1) is a special type referred to as a "Faltung" integral (literally: a folding integral) by

G. Doetsch (1943). Equation (1) may be written.

$$M(t) = M(0)\, F(t) + F^*R\,,$$

where F^*R is the abbreviation for the integral. If we multiply through by exp $(-st)$ and integrate from 0 to ∞, we have

$$\int_0^\infty M(t)\, e^{-st}\, dt = M(0) \int_0^\infty F(t)\, e^{-st}\, dt + \int_0^\infty \int_0^t R(\theta) F(t-\theta) e^{-st}\, dt\, d\theta. \tag{5}$$

The conditions on the functions in order that these integrations are permissible are discussed by G. Doetsch (1943). We shall assume that the integrations are allowed. By definition the integral on the left of equation (5) represents the Laplace transform of $M(t)$ which we shall call $m(s)$; the first integral on the right is the transform of $F(t)$ multiplied by $M(0)$, that is, $M(0)\ f(s)$. The double integral on the right is the transform of the "Faltung" integral. G. Doetsch (1943) shows that the transform of F^*R is equal to the product of the individual transforms, or

$$L\{F^*R\} = L(F) \cdot L(R) = f(s)\ r(s).$$

Hence equation (5) may be written as

$$m(s) = M(0)\ f(s) + f(s)\ r(s), \tag{6}$$

where the lower case letters represent the transforms of the corresponding functions in capitals. An alternate statement is that equation (1) transforms into equation (6). If we seek $f(s)$ we have simply

$$f(s) = \frac{m(s)}{M(0) + r(s)}. \tag{7}$$

It may happen that the particular form of the right side of equation (7) is one of the many Laplace transforms which have been tabulated or that it may be expressed in standard form through algebraic manipulation. If either circumstance exists, we may read directly from tables of transforms given, for example, in G. Doetsch (1943), H. S. Carslaw and J. C. Jaeger (1941), R. V. Churchill (1944), or N. W. MacLachlan (1939), the function $F(t)$ which we seek. If the right side is not a standard form, integration in the complex plane is required. The inverse transform is

$$F(t) = \frac{1}{2\pi i} \int_c e^{st} f(s)\, ds.$$

Details of the integration may be found in the texts mentioned above.

Applying the Laplace transform technique to equation (4), we have

$$\int_0^\infty e^{-st} M(t)\, dt$$

$$= M(0) \int_0^\infty e^{-st}(1 - ct)\, dt - k \int_0^t \int_0^\infty M(\theta)\, [1 - c(t - \theta)]\, e^{-st}\, d\theta\, dt.$$

These integrations are easily performed or the transforms may be read directly from a table:

$$m(s) = \frac{m(0)}{s} - \frac{c\, m(0)}{s^2} - \left(\frac{k}{s} - \frac{k\, c}{s^2}\right) m(s).$$

This equation may be written in terms of $m(s)$ with the right side in a standard form,

$$m(s) = m(0) \left[\frac{A}{s + \alpha} + \frac{B}{s - \beta}\right]$$

where

$$\alpha = \tfrac{1}{2}(k \pm \sqrt{k^2 + 4\, k\, c}), \qquad A = \frac{\alpha + c}{2\,\alpha - k},$$

$$\beta = \tfrac{1}{2}(-k \pm \sqrt{k^2 + 9\, k\, c}), \qquad B = \frac{\alpha - k - c}{2\,\alpha - k}.$$

Consulting G. Doetsch's (1943) table again we find the inverse transforms to be

$$M(t) = M(0)\, [A\, e^{-\alpha t} + B\, e^{\beta t}]. \tag{8}$$

Equation (8) describes behavior of a system in which a first order reaction is taking place and, at the same time, the reacting material is being transported away at a constant rate. It is evident, too, that equation (8) reduces to equation (3) when $c = 0$.

The system described by equation (8) seems useful in biology. For example, the breakdown of glucose in tissue may be considered with some approximation to follow a first order law. Hence a piece of muscle tissue in vitro bathed continuously in a glucose–free solution would be an example of such a system where $M(t)$ would refer to the concentration of glucose.

A large number of biological systems under normal conditions are characterized by the fact that the amounts of certain metabolites remain constant. In terms of equation (1), we have for each such metabolite

$$M\,[1-F\,(t)] = \int_0^t R(\theta)\,F(t-\theta)\,d\,\theta\,, \qquad (9)$$

where M is the constant amount present.

The procedure from this point is determined by what additional information we have. For example, we may know or suspect that the rate at which material enters the system is constant; our problem becomes one of determining the F-function. The resulting equation is easily shown to have the solution $F(t) = \exp\,(-R/M)\,t$. Thus a system in which the amount is constant is characterized by an exponentially decreasing metabolizing function. The converse of this problem is also of biological interest. It is interesting to note that a metabolizing system with a constant amount and a constant F–function is impossible, for assuming that $R(t)$ is a well-behaved function, this system would require

$$\int_0^t R(\theta)\,d\,\theta = \text{constant}\,,$$

which is not possible.

The rate of change of the amount of the metabolite may be found from equation (1) by differentiating,

$$\frac{d\,M(t)}{d\,t} = M(0)\,\frac{d\,F}{d\,t} + \int_0^t R(\theta)\,\frac{\partial\,F(t-\theta)}{\partial\,t}\,d\,\theta + R(t)\,F(0)\,. \qquad (10)$$

This equation is of additional interest, for it may be used as the integral equation of the second kind for determining $R(t)$.

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ERRATA

In the paper "Chain Processes and Their Biophysical Applications: Part I. General Theory" by I. Opatowski, Volume 7, pp. 161-180, on page 177 equation (38) should read:

$$Y_{0,n}/k_j = Y_{0,j-1}{}^{*}Y_{j,n} ;$$

equation (40) should read:

$$Y_{0,n}/(k_j k_m k_p \ldots k_q) = Y_{0,j-1}{}^{*}\, Y_{j,m-1}{}^{*}\, Y_{m,p-1}{}^{*} \ldots {}^{*}\, Y_{q,n}.$$

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